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93 **LYMPHOTOXIN(LT)-α IS A LIGAND FOR THE HERPES VIRUS ENTRY MEDIATOR (HVEM), A MEMBER OF THE TNF RECEPTOR FAMILY INVOLVED IN ACTIVATION OF T AND B CELLS.** **D. MAURI*, K. Kochel*, T. C. Cheung*, R. Montgomery†, R. J. Eisenberg‡, G.H. Cohen‡, P. G. Spear†, and C.F. Ware***

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The Herpes virus entry mediator (HVEM), a member of the tumor necrosis factor receptor (TNFR) superfamily, allows infection of activated T cells by herpessimplex virus (HSV)-1 and 2 by attachment to the envelope glycoprotein D (gD). Here, we demonstrate that HVEM is a receptor for secreted LTα. Signaling through HVEM co-stimulates T cell proliferation and B lymphoblast survival. TNFR associated factors (TRAF)2, 3 and 5 bind to the cytoplasmic domain of HVEM and may induce NFκB activation. Furthermore, the direct competition of herpesvirus envelope glycoprotein D (gD) for cellular HVEM-LT binding characterizes gD as a virokine. These results suggest a mechanism by which HSV alters immune functions regulated by the lymphotoxin system that may allow infection in an immunocompetent host.

94 INVOLVEMENT OF *fas* LIGAND (*FASL*) IN LPS-INDUCED SEPTIC SHOCK USING *fas*-DEFICIENT MRL-*lpr/lpr* MICE: CONCOMITANT PROINFLAMMATORY EFFECTS WITH TNFα. D. Colagiovanni[1], R. Ksontini[2], R. Evans[1], G. Kieft[1], T. Kohno[1], J. Spellberg[1], T. Zhou[3], J. Mountz[3], S. Wooden[4], U. Selvanayagam[4], S. Hu[4], M. Clare-Salzler[2], H. Bluethmann[5], L. Moldawer[2], and C. K. Edwards, III[1]. [1]Amgen, Inc., 3200 Walnut Street, Boulder, CO 80301-2546, [2]Dept. of Surgery, Univ. of FL, College of Med., Gainesville, FL 32610, [3]Dept. of Med., Univ. of AL at Birmingham, Birmingham, AL 35294, [4]Amgen, Inc., 1840 DeHavilland Drive, Thousand Oaks, CA 91320-1789 and [5]F. Hoffman-La Roche, Ltd., Basel Switzerland.

Tumor necrosis factor-α (TNFα) plays a pivotal role in the host response to acute and chronic inflammation. Cytokines of the TNF receptor-ligand family, including TNF-R1 and *fas* (also known as Apo-1 or CD95), are classic triggers of programmed cell death and apoptosis. TNFα and *fas* Ligand (*fas*L; also known as Apo-1L or CD95L) induce apoptosis by binding to their respective "death domain" containing receptors, TNF-R1 and *fas*. We have previously shown that *fas*-deficient MRL-*lpr/lpr* mice sensitized with D-galactosamine ($D\text{-}GalNH_2$) are highly susceptible to *E. coli* lipopolysaccharide (LPS). In this study, we demonstrate that MRL-*lpr/lpr* mice and MRL-+/+ littermates are susceptible to LPS-induced lethal shock which can be inhibited by pre-treatment with a novel recombinant human TNF-binding protein (TNFbp). C57BL/6.TNF-R1 ^{00} knockout and C57BL/6.TNF-R1 ^{00}; *lpr/lpr* double-knockout mice were completely resistant to $LPS/DGalNH_2$ challenge. Since MRL-*lpr/lpr* mice constituitively over-express *fas*L, a mammalian-derived murine *fas* IgG_1 fusion protein, or TNFbp+m*fas* IgG_1 were evaluated. MRL-*lpr/lpr* mice pretreated with suboptimal doses of TNFbp (25 μg/kg) and a novel, mammalian-derived, murine *fas* IgG_1 fusion protein (25 μg/kg), were observed to have enhanced survival (χ^2=0.05) through *48 hr in comparison to either TNFbp-treated, m*fas* IgG_1-treated or diseased controls. *Fas*L activity was due to a short-range autocrine/paracrine mechanism(s) since elevated serum levels could not be detected, although PMϕ and liver *fas*L mRNA levels obtained from $LPS/DGalNH_2$-challenged mice pretreated with TNFbp+m*fas*IgG_1 were reduced. Our findings suggest that susceptibility of MRL-*lpr/lpr* mice to lethal shock is mainly mediated by TNFα and *fas*L, and that TNF/*fas*L-dependent lethality can be prevented by high-affinity TNFα and *fas*L antagonists.

95 IN VITRO CHARACTERISATION OF IL-15 AS A MEMORY FACTOR FOR ACTIVATED CD4 T LYMPHOCYTES. H. Dooms, M. Desmedt, S. Vancaeneghem, P. Rottiers, W. Fiers and J. Grooten, Flanders Interuniversity Inst., Dept. Molecular Biology, B-9000 Gent, Belgium.

Immunological memory is a long-term state of enhanced immunity against a previously encountered antigen (Ag). This augmented responsiveness is presumed to be dependent on the presence of increased frequencies of long-living, optimally reactive, antigen-specific T and B lymphocytes which survived the massive deletion through apoptosis that concludes the primary immune response. Applying both *in vitro* propagated as well as freshly isolated murine T lymphocytes, we show that IL-15, until now mainly considered to be a growth factor for CD8 T cells, exerts memory-promoting functions by signaling for quiescence, long-term survival and optimal secondary responsiveness in CD4 T cells. Thus, IL-15 prevented activation-induced cell death, triggered by immobilized anti-CD3 antibodies or induced following stimulation with Ag in presence of antigen-presenting cells, hereby promoting survival of the TCR-activated T cells. In addition, IL-15 turned off the program of cell death induced by growth factor (IL-2) withdrawal. This survival with IL-15 was not accompanied by proliferation but instead by an arrest of the cells in G1, indicating that IL-15 induced a resting phenotype. Finally, restimulation of these IL-15 treated, resting T cells with Ag resulted in strongly enhanced proliferative responses compared to cells cultured throughout with IL-2. Combining these different IL-15 activities in a single experimental setup produced a response course that featured on the one hand, the long-term survival of CD4 effector cells, generated from the primary antigenic stimulation, as resting, growth factor independent lymphocytes, and, on the other hand, optimal responsiveness of these cells upon renewed TCR triggering. This behavior closely resembles the evolution of immune reactivity in the animal, thus implying IL-15 acts as a memory factor for CD4 T lymphocytes.

96 STUDIES ON THE MECHANISMS OF THE ANTI-APOPTOTIC EFFECTS OF INTERLEUKIN 7 ON HUMAN ACTIVATED T CELLS. C.L.Amos, B.L.Brown, N.Ødum[1] and P.R.M.Dobson[2], Dept. Human Metabolism & Clin. Biochem. and [2]Institute for Cancer Studies, Univ. Sheffield Med. Sch., Sheffield S10 2RX, and [1]Institute of Med. Microbiol. and Immunol., Univ. Copenhagen.

Apoptosis plays an important role in the regulation of development, differentiation and homeostasis in the immune system. Immunological memory depends on the rescue of some activated T-lymphocytes from apoptosis. Factors produced by other T-lymphocytes or stromal cells, for example the cytokines (interleukin-2, -4, -7 and -15), affect the balance of apoptosis and proliferation. We have examined the effect of Interleukin-7 (IL-7) on apoptosis induced by dexamethasone and cytokine withdrawal in IL-2 dependent, primary activated human T cells. Interleukin 7 (like IL-2) rescued cells from apoptosis as measured by their DNA profile and fragmentation. These cytokines prevented the glucocorticoid-induced cleavage of the caspase 3 substrate PARP and of a specific fluorogenic substrate. Interleukin 7 also upregulated the expression of $bclx_L$ and bcl-2, measured by Western blotting, and counteracted the downregulation of these anti-apoptotic proteins induced by the synthetic glucocorticoid dexamethasone. However bcl-2 was expressed at a much lower level than $bclx_L$, indicating a potentially more important role of $bclx_L$ in these cells. Levels of the pro-apoptotic protein, bax, did not significantly change on cytokine stimulation or dexamethasone treatment. Interestingly, an unknown 23kDa band which was recognised by the anti-bcl-2 antibody was induced by dexamethasone and suppressed by IL-7 and IL-2. This study shows a clear role for IL-7 as a survival factor for glucocorticoid-induced apoptosis. It also suggests that regulation of $bclx_L$ and inhibition of caspase 3 activity may predominantly mediate this rescue signal.

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